TABLE 261e-4 COMPLICATIONS FROM 438,134 ADMINISTRATIONS OF VACCINIA DURING THE U.S. DEPARTMENT OF DEFENSE (DOD) SMALLPOX IMMUNIZATION CAMPAIGN INITIATED IN DECEMBER 2002

Complication	Number of Cases	DoD Rate per Million Vaccinees (95% Confidence Interval)	Historic Rate Per Million Vaccinees
Mild or temporary:			
Generalized vaccinia, mild	35	67 (52, 85)	45–212[a]
Inadvertent inoculation, self	62	119 (98, 142)	606[a]
Vaccinia transfer to contact	28	53 (40, 69)	8–27[a]
Moderate or serious:			
Encephalitis	1	2.2 (0.6, 7.2)	2.6–8.7[a]
Acute myopericarditis	69	131 (110, 155)	100[b]
Eczema vaccinatum	0	0 (0, 3.7)	2–35[a]
Progressive vaccinia	0	0 (0, 3.7)	1–7[a]
Death	1[c]	1.9 (0.2, 5.6)	1–2[a]

[a]Based on adolescent and adult smallpox vaccinations from 1968 studies, both primary and revaccinations. [b]Based on case series in Finnish military recruits given the Finnish strain of smallpox vaccine. [c]Potentially attributable to vaccination; after lupus-like illness.

Source: From JD Grabenstein and W Winkenwerder: *http://www.smallpox.mil/event/SPSafetySum.asp.*

Vaccination and Prevention In 1796, Edward Jenner demonstrated that deliberate infection with cowpox virus could prevent illness on subsequent exposure to smallpox. Today, smallpox is a preventable disease following immunization with vaccinia. The current dilemma facing our society regarding assessment of the risk and benefit of smallpox vaccination is that the degree of risk that someone will deliberately and effectively release smallpox into our society is unknown. Given that there are well-described risks associated with vaccination, the degree of risk/benefit for the general population does not favor immunization. As a prudent first step in preparedness for a smallpox attack, however, members of the U.S. armed services received primary or booster immunizations with vaccinia before 1990 and after 2002. In addition, a number of civilian health care workers who comprise smallpox-response teams at the state and local public health level have been vaccinated.

Initial fears regarding the immunization of a segment of the American population with vaccinia when there are more individuals receiving immunosuppressive drugs and other immunocompromised patients than ever before were dispelled by the data generated from the military and civilian immunization campaigns of 2002–2004. Adverse event rates for the first 450,000 immunizations were similar to and, in certain categories of adverse events, even lower than those from prior historic data, in which most severe sequelae of vaccination occurred in young infants (Table 261e-4). In addition, 11 patients with early-stage HIV infection were inadvertently immunized without problem. One significant concern during that immunization campaign, however, was the description of a syndrome of myopericarditis, which had not been appreciated during prior immunization campaigns with vaccinia. In an effort to provide a safer vaccine to protect against smallpox, ACAM 2000, a cloned virus propagated in tissue culture, was developed and became the first second-generation smallpox vaccine to be licensed. This vaccine is now the only vaccinia product currently licensed in the United States and has been used by the U.S. military since 2008. It is part of the U.S. government stockpile. Research continues on attenuated forms of vaccinia such as modified vaccinia Ankara (MVA). Vaccinia immune globulin is available to treat those who experience a severe reaction to immunization with vaccinia.

TULAREMIA

See also Chap. 195.

***Francisella tularensis* as a Bioweapon** Tularemia has been studied as an agent of bioterrorism since the mid-twentieth century. It has been speculated by some that the outbreak of tularemia among German and Soviet soldiers during fighting on the Eastern Front during WWII was the consequence of a deliberate release. Unit 731 of the Japanese army studied the use of tularemia as a bioweapon during WWII. Large preparations were made for mass production of *F. tularensis* by the United States, but no stockpiling of any agent took place. Stocks of *F. tularensis* were reportedly generated by the Soviet Union in the mid-1950s. It has also been suggested that the Soviet program extended into the era of molecular biology and that some strains were engineered to be resistant to common antibiotics. *F. tularensis* is an extremely infectious organism, and human infections have occurred from merely examining an uncovered petri dish streaked with colonies. Given these facts, it is reasonable to conclude that this organism might be used as a bioweapon through either an aerosol or contamination of food or drinking water.

Microbiology and Clinical Features Although similar in many ways to anthrax and plague, tularemia, also referred to as rabbit fever or deer fly fever, is neither as lethal nor as fulminant as either of these other two category A bacterial infections. It is, however, extremely infectious, and as few as 10 organisms can lead to establishment of infection. Despite this fact, it is not spread from person to person. Tularemia is caused by *F. tularensis*, a small, nonmotile, gram-negative coccobacillus. Although it is not a spore-forming organism, it is a hardy bacterium that can survive for weeks in the environment. Infection typically comes from insect bites or contact with organisms in the environment. Infections have occurred in laboratory workers studying the agent. Large waterborne outbreaks have been recorded. It is most likely that the outbreak among German and Russian soldiers and Russian civilians noted above during WWII represented a large waterborne tularemia outbreak in a *Tularensis*-enzootic area devastated by warfare.

Humans can become infected through a variety of environmental sources. Infection is most common in rural areas where a variety of small mammals may serve as reservoirs. Human infections in the summer are often the result of insect bites from ticks, flies, or mosquitoes that have bitten infected animals. In colder months, infections are most likely the result of direct contact with infected mammals and are most common in hunters. In these settings, infection typically presents as a systemic illness with an area of inflammation and necrosis at the site of tissue entry. Drinking of contaminated water may lead to an oropharyngeal form of tularemia characterized by pharyngitis with cervical and/or retropharyngeal lymphadenopathy (Chap. 195). The most likely mode of dissemination of tularemia as a biologic weapon would be as an aerosol, as has occurred in a number of natural outbreaks in rural areas, including Martha's Vineyard in the United States. Approximately 1–14 days following exposure by this route, one would expect to see inflammation of the airways with pharyngitis, pleuritis, and bronchopneumonia. Typical symptoms would include the abrupt onset of fever, fatigue, chills, headache, and malaise (Table 261e-3). Some patients might experience conjunctivitis with ulceration, pharyngitis, and/or cutaneous exanthems. A pulse-temperature dissociation might be present. Approximately 50% of patients would show a pulmonary infiltrate on chest x-ray. Hilar adenopathy might also be present, and a small percentage of patients could have adenopathy without infiltrates. The highly variable presentation makes acute recognition of aerosol-disseminated tularemia very difficult. The diagnosis would likely be made by immunohistochemistry, molecular techniques, or culture of infected tissues or blood. Untreated, mortality rates range from 5 to 15% for cutaneous routes of infection and from 30 to 60% for infection by inhalation. Since the advent of antibiotic therapy, these rates have dropped to <2%.

TREATMENT TULAREMIA

Both streptomycin and doxycycline are licensed for treatment of tularemia. Other agents likely to be effective include gentamicin, chloramphenicol, and ciprofloxacin (Table 261e-3). Given the potential for